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HELICOBACTER PYLORI AND THE GUT

Low *Helicobacter pylori* eradication rates with 4- and 7-day regimens in an Iranian population

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Abstract

Background: In Iran, there is insufficient information on the efficacy of *Helicobacter pylori* eradication regimens shorter than 10 days. This study aims at assessing the efficacy of 4- and 7-day *H. pylori* eradication regimens in a high-incidence area of gastric cancer in Iran.

Methods: Subjects with an endoscopic diagnosis of gastritis, positive urease test, and a histological diagnosis of chronic gastritis were enrolled. Patients were randomly assigned to one of three groups: AOC7 (1000 mg amoxicillin, 20 mg omeprazole, and 500 mg clarithromycin twice daily for 7 days), FOT4 (200 mg furazolidone, 20 mg omeprazole, and 500 mg tetracycline twice daily for 4 days) and FOT7 (the same treatment as the FOT4 group but for 7 days). Sensitivity to these antibiotics was determined in all isolates recovered from culture. The efficacy of eradication was assessed 8 weeks after the end-of-treatment by the ^{14}C-urea breath test.

Results: One hundred and twenty-eight patients were enrolled in the study. Culture was positive for 84 patients and none of these were resistant to amoxicillin, tetracycline or furazolidone, 1.2% were resistant to clarithromycin and 32.1% to metronidazole. Forty-five, 41 and 42 patients were randomly allocated to the AOC7, FOT4, and FOT7 groups, respectively. The intention-to-treat eradication rates were 35.5, 17.1, and 23.8% for the AOC7, FOT4, and FOT7 groups, respectively.

Conclusion: Treatment regimens of 4 or 7 days are unacceptable for *H. pylori* infection in Iran, even in the presence of a favorable sensitivity profile.

Key words: *Helicobacter pylori*, Iran, therapeutics.

INTRODUCTION

Helicobacter pylori eradication is now well established as the first line of therapy for peptic ulcer disease.[1] *Helicobacter pylori* eradication was found to be ineffective in treating non-ulcer dyspepsia, and the ideal therapy for this entity is still debated. The role of *H. pylori* eradication in reduction of the long-term risk of gastric carcinoma is also not clear.[2] Although, a recent study from Japan by Uemura *et al.*, which is the first long-term prospective comparison between *H. pylori*-infected and non-infected patients, has shown that non-ulcer dyspepsia patients with *H. pylori* infection have a near 5% risk of developing gastric cancer during an 8-year follow up.[3] Therefore, *H. pylori* eradication may be indicated in non-ulcer dyspepsia on the basis of the risk of gastric cancer alone.[4]

Gastric cancer is the second most common cause of cancer-related mortality in the world,[5,6] and is the most common gastrointestinal malignancy in Iran (AR Sajjadi, unpubl. data, 2000).[7] Ardabil province, northwest of Iran, was reported to have the highest incidence

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of gastric cancer throughout the country, with an incidence rate of 48.90 and 26.77 per 100 000 per year in men and women, respectively. This constitutes 30% of all types of malignancy in this province (AR Sajjadi, unpubl. data, 2000). The prevalence of *H. pylori* infection is approximately 95% in Ardabil. If *H. pylori* eradication proves to be justified for prevention of gastric carcinoma, which seems very likely, the selection of a nonexpensive, safe, and effective antibiotic regimen is very important. Decreasing the cost of eradication can be accomplished by using cheaper medications, and/or reducing the total duration of antibiotic therapy while maintaining a high eradication rate.

In an attempt to decrease the cost of eradication, many investigators have tried shorter courses of treatment with various success rates. A shorter course is also easier to comply with. Many studies, notably those from Europe, have very good success rates with courses as short as 3 days.[8–13] In contrast, other studies do not.[14–16]

In this study, we have compared the efficacy of three 4- and 7-day *H. pylori* eradication regimens in patients with chronic gastritis from Ardabil.

METHODS

The study was performed in conjunction with a pilot endoscopic cancer-screening survey in Ardabil. The cancer-screening pilot included a random selection of 500 individuals, 40-years-old or older, living in the Ardabil district. From these patients, we selected all consenting subjects with an endoscopic diagnosis of corpus predominant gastritis, positive rapid urease test, and a histological diagnosis of *H. pylori*-related chronic gastritis who underwent endoscopic evaluation during a 3-day period. The study was approved by the ethics committee of the Department of Internal Medicine of Tehran University of Medical sciences.

The enrolled patients were then randomly allocated to one of three groups. The AOC7 group was treated with 1000 mg amoxicillin, 20 mg omeprazole, and 500 mg clarithromycin twice daily for 7 days. The FOT4 group was treated by 200 mg furazolidone, 20 mg omeprazole, and 500 mg tetracycline twice daily for 4 days. The FOT7 group received the same treatment as the FOT4 group but for 7 days. The AOC7 combination was chosen because of reports of its high success in various studies, sometimes with other proton pump inhibitors (PPI) used instead of omeprazole.[10–12] The FOT4 and FOT7 combinations were selected because of our previous experience in Iran showing that furazolidone is a cheap and effective substitute for clarithromycin.[17] *Helicobacter pylori* culture was performed for all isolates, and sensitivity tests were performed for culture-positive isolates.

Based on previous reports, we were expecting an 85% eradication rate.[8–13] To have a power of 80% to detect a 20% difference in eradication rates, 40 cases would be required in each group.

Biopsies from the antrum were cultured on brucella agar supplemented with 5–7% sheep blood, amphotericin B (6 mg/L), vancomycin (10 mg/L), trimethoprim (5 mg/L), and polymixin B (2500 IU/L). Sensitivity to metronidazole, furazolidone and clarithromycin was determined by agar dilution,[18] and sensitivity to amoxicillin and tetracycline by the disc diffusion method.[19] Resistant strains were defined as those that grew on the egg yolk agar medium containing more than 8 g/mL metronidazole, 2 μg/mL clarithromycin, or 0.5 μg/mL furazolidone, and those with a growth-inhibition zone diameter of equal or less than 13 mm for amoxicillin and 14 mm for tetracycline.[20]

Patients were given both verbal and written instructions about the importance of taking the medications regularly and not to stop medication on the event of mild side-effects. They were also instructed to report moderate or severe side-effects to one of the two local members of the research team.

For the assessment of compliance and side-effects, all cases were visited 10 days after the start of therapy. Compliance was assessed by the percentage of medications used. It was considered excellent, good, or poor when 90, 80, or 70% of the provided medicine was taken by the patient, respectively. Side-effects were evaluated by direct questioning at the same visit. The efficacy of eradication was assessed 8 weeks after the end of treatment by the ^{14}C-urea breath test as described by Raju *et al.*[21]

RESULTS

One-hundred and twenty-eight patients were enrolled in the study. Seventy-seven patients (60%) had occasional dyspepsia defined as mild epigastric discomfort at least once a week. The other subjects had no gastrointestinal symptoms. Forty-five, 41 and 42 patients were randomly allocated to the AOC7, FOT4, and FOT7 groups, respectively. The demographic characteristics of the patients in all three groups were comparable and are given in Table 1. On endoscopic examination, no patient had peptic ulcers, erosions or findings other than described by the endoscopist as gastritis. Forty-six (36%) of our patients were found to have gastric atrophy on histological examination, and 12 (9%) had intestinal metaplasia.

Cultures were positive in 84 cases. None of the positive cultures were resistant to amoxicillin, furazolidone or tetracycline, 1.2% were resistant to clarithromycin and 32.1% to metronidazole. There were no significant differences in antibiotic sensitivity between the three groups. The compliance was excellent in all patients. There were no significant differences in compliance between the three groups. Side-effects were mild and no patient discontinued medication because of side-effects. A few side-effects (bad taste, nausea, oral ulcers), were significantly more common in the FOT7 group.

Eighteen patients were lost on the follow-up visit for evaluating the eradication rate. The per-protocol eradication rates were 42.1, 20.6 and 29.4% for the AOC7, FOT4, and FOT7 groups, respectively, and the intention-to-treat rates were 35.5, 17.1, and 23.8%, respectively. The difference between the eradication rates was only marginally significant between the AOC7

Table 1 Baseline demographic and clinical characteristics of patients who participated in the *Helicobacter pylori* eradication trial in Ardabil province, Iran

	AOC7	FOT7	FOT4
No. patients	45	42	41
Male/female	17/28	21/21	25/16
Mean age ± SD (years)	55.07 ± 10.84	52.41 ± 9.18	51.78 ± 9.14
Age range (years)	40–73	40–73	40–69
Smoker (> 10 cigarettes/day)	7	4	5
Non-steroidal anti-inflammatory drug use	9	6	6

and FOT4 groups ($P = 0.044$ for per-protocol, and $P = 0.045$ for intention-to-treat).

DISCUSSION

Helicobacter pylori eradication using short-term regimens is highly attractive because of the cheaper cost and better patient compliance involved. Many studies have evaluated shorter courses of regimens proven to be effective when given for 10 or 14 days.[8,10–12,22–24] The AOC combination is one such regimen, and many studies confirm its efficacy when given for 4 or 7 days. Furazolidone-based regimens have also been shown to be very effective and less expensive substitutes for clarithromycin-based regimens.[22,23,25–27] There are also a few studies reporting relatively good results with 7-day courses of furazolidone-based regimens.[22,23]

In Iran, many studies have addressed the issue of the optimal treatment for *H. pylori* eradication. Most studies from Iran have evaluated treatment regimens of 10 days or more, and the eradication rate in ulcer patients has been shown to be lower than similar reports from Europe, America and China.[14,17,25,28–30] Studies on short-term treatments in Iran have reported very poor results. In a recent report, a 7-day regimen in patients with duodenal ulcers resulted in an unacceptable eradication rate of 23.8%. This study used bismuth, amoxicillin, metronidazole, and ranitidine. The same regimen resulted in an eradication rate of 62.5% when given for 2 weeks.[14]

In the present report, we demonstrate that 4- and 7-day courses of a furazolidone-based, and a 7-day course of a clarithromycin-based regimen are clearly inefficient, even though we have a favorable *H. pylori* sensitivity.

Our sample size was computed to provide a power of 80%, assuming an 85% eradication rate. However, with the unexpectedly low eradication rates obtained (mean 31%), the power of our study for detecting differences between each treatment group would be too low (approximately 65% for a 20% difference). The major point of our study is the unacceptably low rates obtained with any of the three regimens.

It should be noted that our patients were without significant symptoms and did not have duodenal or gastric ulcers. It is well known that eradicating *H. pylori* in this setting is more difficult.[23,31] Studies evaluating eradication rates of *H. pylori* in non-ulcer dyspepsia usually report rates 10–15% less than those in patients with ulcers.[23,31] But the eradication rates we have obtained in this study are much less. All our subjects had excellent compliance, so the reason for this low eradication rate should lie elsewhere.

Differences between infecting strains of *H. pylori* have already been shown to be important in the efficacy of eradication.[32] Low eradication rates in non-ulcer patients may be linked to the CagA status of isolates. CagA-positive strains are more prevalent in ulcer patients than in non-ulcer patients.[33] Furthermore, less virulent strains (CagA negative, Vac S2) are more difficult to eradicate than the more virulent strains (CagA positive, Vac S1).[34]

Ardabil is a high-prevalence area for gastric cancer. Considering the known association of gastric cancer with *H. pylori* infection, it is likely that the *H. pylori* strains associated with gastric cancer are biologically different from those that are not. It is probable that the cancer-associated *H. pylori* is more difficult to treat.

Further research into the phenotype of the *H. pylori* strain and the profile of host-immune response is necessary in order to explain the very low eradication rate we encountered in Ardabil.

Another probable reason for the low eradication rates may lie in the fact that, in an endemic area such as Ardabil, there may be a higher load of bacteria in the gastric mucosa.[35] We have already shown that *H. pylori* infection in Ardabil is acquired at a younger age. In a study of patients younger than 14 years old, 47.5% of subjects from Ardabil were infected as compared with 30.6% from Yazd, a city in central Iran with a low incidence of gastric cancer.[36] Higher densities of *H. pylori* in gastric mucosa may have resulted from acquiring infection at an earlier age with a less virulent strain, resulting in poor host-immune response. Such an infection is difficult to eradicate with 4- or 7-day regimens and further trials with bismuth-based quadruple therapies of at least 10-day duration are warranted. Eradication may also need to be started earlier in life in order to be more effective.

In conclusion, the 4- and 7-day PPI-based triple therapies used in this study, in spite of the good sensitivity profile, do not seem to be effective in this population and should not be used.

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